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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/619,285	GYURIS ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-34, 49-91* is/are pending in the application.

4a) Of the above claim(s) *34 and 89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-33,49-88,90 and 91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/26/2004 has been entered.

Claims 28, 49, 50, 51, 53, 65-68, 70, 71, 75-78, 80-91 are amended.

Claims 34 and 89 as currently construed are dependent on base claims 28, 49, or 50, drawn to nucleic acid. However, claims 34 and 89 are drawn to polypeptide. Prosecution history indicates that restriction was made between nucleic acid and polypeptide in the Office action mailed on 10/02/2001; applicant elected group II, drawn to nucleic acids; and the Office made the restriction Final in the Action mailed on 04/09/2002. The Action mailed on 04/09/2002 at page 4, paragraph 6 and all subsequent Actions have indicated that all elected claims have been interpreted as drawn to nucleic acid, for example, the Action mailed on 09/26/02 at page 3 also interpreted claims 34 and 89 drawn to nucleic acid. Applicant has not raised the issue of claims 34 and 89 being drawn to polypeptide, not nucleic acid so far in the prosecution history.

During the interview (see the attached interview summary), applicant was given a choice of either amending claims 34 and 89 to reflect the election or the claims being withdrawn from further consideration. Applicant declined to amend claim 34.

Therefore, as indicated during the interview, claims 34, and 89, drawn to polypeptide are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. It is noted that claims 34 and 89 as currently construed depend on base claim 28, 49, or 50. However, the base claims are drawn to nucleic acid, and claim 34 uses claims 28, 49, and 50 as identifier of what kind of polypeptide is being claimed. In other words, claims 34 and 89 does not include the limitation (nucleic acids) of base claims.

Claims 28-34, and 49-91 are pending.

Claims 28-33, 49-88, 90, and 91 are examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

This Office action contains new grounds of rejection.

Claim Rejections - 35 USC § 103, Withdrawn

The rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over WO 95/30759 (AB of IDS, Paper No. 14, publication date: 11/16/1995) is withdrawn in view of the new ground of rejection below under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over WO 95/30759. Applicant's arguments will be addressed in the rejection under 35 U.S.C. 35 USC § 102/103 below.

Double Patenting

Claims 28-33, 49-88, 90, and 91remain provisionally rejected for reason of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-33, and 54-104 of copending Application No. 09/768,183

because applicant has not filed terminal disclaimer. It is noted that applicant will file a terminal disclaimer when the claims are indicated allowable except this issue.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 28-33, and 49-88, 90, and 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims set forth in Paragraph 3 of the Office action mailed on 4/9/2002 is reinstated. The base claims 28, 49, 50, 75 recite several specific residues of serum albumin, for example, "residues 360-369" in line 3 of claim 28, but it is not clear what the metes and bounds are. Applicant argued at page 10 of the amendment filed on 07/05/2002 that based on disclosure at pages 35-36 of the specification, as well as at Fig. 1 which illustrates the 3-D space-filling model of human serum albumin, and that the protein sequences of the highly conserved human and mouse serum albumin are well known in the art before the filing of the instant application, a skilled artisan would readily understand that residues 360-369 refers to the mature serum albumin residues. This argument has been fully considered but not persuasive for following reasons.

First, the scope of the invention is not limited to human or mouse serum albumin but the instant application at page 8 says that serum albumin is intended to include all kinds of serum albumin but the specification does not reasonably teach which amino acids of a serum albumin sequence is a reference sequence. It appears that the art

does not recognize a unified nomenclature designating how each amino acid of a serum albumin should be numbered. This means residues 360-369 of a serum albumin could mean many different residues for a different serum albumin. For example, Carter and He (IDS AE filed on 6/05/2002, 1994, Advanced in Protein Chemistry 45, pages 153-203) at page 160, lines 4-9 teach that there are more than one nomenclatures being used for various serum albumins and the authors of the review articles define that all of the residue designation of serum albumin is normalized to HSA (human serum albumin). Carter and He (IDS AE filed on 6/05/2002, 1994, Advanced in Protein Chemistry 45, pages 153-203) at Table II at pages 158-9 teach that serum albumins have different lengths, for example, the serum albumin in the last row of Table II has 4 more amino acids just before h5 (II) as compared to human serum albumin. Therefore, one would have difficulty to determine whether inserting a biologically active peptide at "residues 356 to 359" of the last row of Table II of Cater and He (cited above) would infringe on the instantly claimed invention. Similar analysis applies for claims 49, 50, and 75. Even if the instantly recited residues refer to mature human and mouse serum albumin protein sequences, applicant's terminology in the instant specification is not consistent with that of art. Thus, it is confusing as to what the recited residues refer to. For example, He and Carter (1992, Nature, vol. 358, pages 209-215) teach that human serum albumin has 28 helices, not "10" as indicated at page 35 line 3 of the specification under the heading "Serum albumin loop regions". The "residues 450-463" recited in instant claim 28 does not appear to be a "loop" as indicated by Fig. 1 of the instant application, but helical region, more specifically helix 4 in domain III according to

Carter and He (Carter and He (IDS AE filed on 6/05/2002, 1994, Advanced in Protein Chemistry 45, pages 153-203). This rejection affects all dependent claims.

Claim 69 recites "similar in line 2 but it is not clear what the metes and bounds are for the limitation.

Claim 79 recites the limitation "the myc epitope" and "the RGD peptide" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 29-33, 49-88, 90, and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This **new matter rejection** is made because the Office is not able to find the support in the specification as originally filed for the several limitations in the base claims 49, 50, and 75.

Claim 49 reads:

> A nucleic acid encoding a chimeric polypeptide having the structure of A-B-C, wherein:
> A represents an N-terminal peptide fragment of serum albumin (SA) terminating in an amino acid corresponding to one of residues **359-368**;
> B represents a biologically active peptide; and,
> C represents a C-terminal peptide fragment of SA beginning from an amino acid corresponding to one of residues **361-370**;
> **wherein A and C do not include overlapping portions of the regions 360-369 and 450-463**, and wherein said peptide is (i) heterologous to said serum albumin; and (ii) interacts with a living organism to induce a change in a biological function of the organism or any part of the organism.

Claim 50 reads:

A nucleic acid encoding a chimeric polypeptide having the structure of A-B-C, wherein:
A represents an N-terminal peptide fragment of serum albumin (SA) terminating in an amino acid corresponding to one of residues **449-462**;
B represents a biologically active peptide; and,
C represents a C-terminal peptide fragment of SA beginning from an amino acid corresponding to one of residues **451-464**;
wherein A and C do not include overlapping portions of the regions 360-369 and 450-463, and wherein said peptide is (i) heterologous to said serum albumin; and (ii) interacts with a living organism to induce a change in a biological function of the organism or any part of the organism.

Claim 75 reads:

A nucleic acid encoding a chimeric polypeptide having comprising serum albumin having at least two biologically active peptides inserted therein, wherein at least one biologically active peptide is inserted (i) between an N-terminal SA sequence ending in one of residues of **359-368** and a C-terminal SA sequence beginning from one of residues from 361-370; or (ii) between an N-terminal SA sequence ending in one of residues 449-462 and a C-terminal SA sequence beginning from one of residues **451-464**; **wherein the N- and C-terminal sequences do not include overlapping portions of the regions 360-369 and 450-463**, wherein said at least two biologically active peptide are (i) heterologous to said serum albumin; and (ii) interacts with a living organism to induce a change in a biological function of the organism or any part of the organism.

The prosecution history indicates that applicant added the base claims 49, 50, and 75 with the amendment filed on December 20, 2001, stating that new claims are supported by the original claims 1-3, and 28, page 35, 3rd paragraph to page 36, 2nd paragraph. The specification at page 35, 3rd paragraph to page 36, 2nd paragraph as well as Fig. 1 has support for "360-369" and "450-463" regions of SA, the support for the bolded limitations above are not found. Original claims 1-3, 28, and page 35, 3rd paragraph to page 36, 2nd paragraph do not have support for the limitations "359-368" (one amino acid moved toward the N-terminal end from loop 360-369 shown at Fig. 1),

"361-370" (one amino acid moved toward the C-terminal end from loop 360-369 shown at Fig. 1), "449-462" (one amino acid moved toward the N-terminal end from loop 450-463 shown at Fig. 1), or "451-464" (one amino acid moved toward the C-terminal end from loop 450-463 shown at Fig. 1).

The original claims 1-3, and 28 read:

1. A chimeric polypeptide comprising serum albumin protein (SA) having a biologically active heterologous peptide sequence inserted therein.

2. A chimeric polypeptide having the structure A-B-C, wherein:
A represents a first fragment of Serum albumin (SA);
B represents a biologically active heterologous peptide sequence; and
C represents a second peptide fragment of SA.

3. A chimeric polypeptide comprising:
a first peptide fragment, comprising a N-terminal fragment of serum albumin(SA) protein; a second peptide fragment, comprising a biologically active heterologous peptide sequence, and a third peptide fragment, comprising a C-terminal fragment of SA.

28. A nucleic acid encoding the chimeric polypeptide of claim 1, 2, or 3.

The original claims 1-3, and 28 have support for making generic chimeric serum albumin but does not have support for the specifically recited residues of serum albumin in claims 49, 50, and 75. The specification as originally filed does not have explicit or implicit support for specifically recited residues as the insertion sites in serum albumin. The specification as originally filed does not specifically points out the insertion sites could be moved one amino acids to N-terminal or C-terminal end from the three loops shown at Fig. 1 of the specification. Further, the specification as originally filed does not have support for the limitation "wherein A and C do not include overlapping portions of the regions 360-369 and 450-463." Applicant is kindly requested to point out the

support in the originally filed specification for the limitations for "359-368" "361-370", "449-462", and "451-464" "wherein A and C do not include overlapping portions of the regions 360-369 and 450-463" since the support is not apparent to the Office. This rejection affects all claims that depend on the rejected base claims.

Claims 30-33, 58, and 88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

This enablement rejection is made because claims 30-33, and 88 recite several retrovirus vectors, such as HIV and also recite cells (see claim 31 for vector, and claim 33 for cells) not commonly used in the art for in vitro protein expression, therefore the invention claimed in claims 30-33, and 88 are interpreted as drawn to gene therapy.

The instant specification is about residues 360-369, especially between residues 364 and 365 are exposed to solvent. The specification does not teach method of gene therapy. The art recognizes that gene therapy is not a trivial matter. The specification does not teach any method of overcoming technical difficulties the art has been facing with the gene therapy. For example, Friedmann (Scientific American, June 1997, pages 96-101), Verma and Somia (1997, Nature, vol. 389, pages 239-242), and Rubanyi (2001, Molecular Aspects of Medicine 22, pages 113-142) all teach that gene therapy art still faces major hurdle to overcome. Rubanyi at the abstract teaches that the prerequisite of successful gene therapy includes "therapeutically suitable genes with a proven role in pathophysiology of the disease". The instant specification fails at this first prerequisite because the specification does not teach any therapeutically suitable genes with a proven role in pathophysiology of the disease. Verma and Somia teach at page 240, first column that critical limitation of retroviral vectors is their inability to infect non-dividing cells such as muscle cells claimed in instant claim 33. The specification does not teach how to use the retroviral vectors in instant claim 31 for the various cells in claim 33. Friedman summaries the current state of gene therapy as "treating disease by providing needed gene remains a compelling idea, but clinical and basic researchers still have much to do before gene therapy can live up to its promise" (note the italicized headline at the top of page 96). The instant specification does not teach a single technical problem being solved for gene therapy art.

Claim 58 is interpreted as drawn to nucleic acid comprising chimeric serum albumin inserted with a useful ligand binding peptide to orphan receptor. Bresnick et

al., (2003, Assay Drug Dev Technol. Vol. 1, pages 239-49, abstract only) teach "orphan receptor" by definition is a receptor without a known ligand and it has to be screened. The specification does not teach how to make a biologically heterologous peptide that binds to an orphan receptor. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to make/use the instantly claimed invention, broad breath of the claims, it is concluded that undue experimentation is required to practice the invention.

Claims 28-33, and 49-88, 90, and 91 ejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the exposed resides of serum album, does not reasonably provide enablement for the buried residues (residues "450-463"). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

This rejection is made because the claimed invention is interpreted as drawn to nucleic acid comprising a chimeric serum albumin with an inserted biologically heterologous peptide buried in said serum albumin.

The specification at pages 35-36 discloses that when a heterologous peptide inserted in SA at residues 467-468 is buried and therefore inaccessible. The specification does not teach how to use the buried heterologous peptide. When the heterologous peptide is buried in serum albumin, it does not appear to exert its biological activity. WO 95/30759 (AB of IDS filed on 06/05/2002, Paper No. 14, publication date: 11/16/1995) at page 6 teaches that one critical element for chimeric serum albumin is accessibility of the inserted heterologous peptide.

Considering the unpredictable state of art, limited guidance, no examples in the specification how to use the instantly claimed invention, broad breath of the claims, it is concluded that undue experimentation is required to practice the full scope of the invention.

Claim Rejections - 35 USC § 102/103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28, 29, 49-57, 59-78, 80-87, 90, and 91 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over **WO 95/30759** (AB of IDS filed on 06/05/2002, Paper No. 14, publication date: 11/16/1995) as evidenced by Carter and He (IDS AE filed on 6/05/2002, 1994, Advanced in Protein Chemistry 45, pages 153-203), He and Carter (1992, Nature, vol. 358, pages 209-215), Takahashi et al., (1987, Proc. Natl. Acad. Sci. USA, vol. 84, pages 8001-8005), and Brennan (1985, Biochim Biophys Acta, vol. 830, pages 320-4, abstract only), Fixe et al (IDS, AJ, 998, Cytokine vol. 10, 32-7), Zetter (IDS, AK, 1998, Annu Rev Med. Vol. 49, pages 407-24), Castells (1994, Allerg Immunol, vol. 26, pages 127-31).

The four of the seven references used as evidence are introduced in this rejection to present what was known about the mature human serum albumin structure in details before the effective filing date of the instant application, since the art of record i.e. WO 95/30759 does not show the structure in detail but refers to the original paper that published the crystal structure of the mature human serum albumin. The Office is compelled to present these references, especially in view of applicant's argument at last paragraph of page 8 to first paragraph of page 9 of the amendment filed on 1/26/2004 that the '759 publication in Fig. 1 shows the entire serum albumin structure and that the '759 publication teaches away from instantly claimed invention. The rest of the references is to show that those heterologous peptides listed in WO 95/30759 are same as the instantly listed heterologous peptides although the art and instant application have different functional descriptions for them.

Claims 28, 29, 49-57, 59-78, 80-87, 90, and 91 are interpreted as drawn to nucleic acid encoding chimeric polypeptide comprising serum albumin with a useful art known heterologous peptide inserted amino acids 360-369, wherein the useful peptide has various sizes from 4 to 400 amino acids (claims 65-68, 80-87, 90, and 91), wherein the chimeric polypeptide exhibits increased in vivo half life (claims 72-74), wherein the useful heterologous peptide is derived from various art-known proteins useful for treating disease or other clinically purposes (claims 51-57, 59-64), wherein the tertiary structure of the chimeric polypeptide is similar to native serum albumin (claim 69), wherein the inserted peptide replaces a portion of native SA sequence (claim 70), the inserted peptide and the taken out piece are not same length (claim 71) .

Based on the unclear definition of serum albumin residue numbering (see claims rejection under 112, second paragraph above) and the broad definition of what constitutes "a biologically active peptide" at page 9 of the specification, claims 28, 29, 49-57, 59-78, 80-87, 90, and 91 read on the nucleic acid encoding chimeric serum albumin of WO 95/30759.

Since the instant application does not disclose any new "biologically active peptide" being inserted in residues of 360-369 of serum albumin and does not teach any new discovery in terms of in vivo stability, the main focus of the analysis is to determine whether residues of 360-369 of serum albumin is the same site as WO 95/30759 teaches or an obvious variation. Applicant argues that '759 publication does not specifically point out the instantly claimed insertion sites in spite of being aware of the crystal structure of human SA, thus '759 publication teaches away form the instantly

claimed insertion sites. From the outset, the Office agrees with applicant's assessment that '759 publication teaches away from residues 450-463 based on what was known about human albumin structure. The '759 publication clearly teaches at pages 6 and 7, one of two main criteria for making a clinically useful chimeric serum albumin protein is to choose sites of SA that allow the heterologous peptide exposed on surface for accessibility. Based on the '759 publication using the crystal structure in He and Carter (1992) as guide (see bottom of page 6 of the 759 publication), residues 450-463 is not obvious site for insertion of a heterologous peptide. However, applicant's argument that '759 publication teaches away from residues 360-369 is unpersuasive because the '759 publication at page 6 teaches that the crystal structure of serum albumin had been solved in 1992 by He and Carter. Figure 1 of the '759 publication is not the entire SA structure but one of the three repetitive domains of human serum albumin. In fact, the diagram shown in Figure 1 of '759 publication is identical to the topological illustration shown Fig. 3 B of He and Carter (1992). The '759 publication at page 7 lines 3-5 teaches that the preferred insertion sites are "exposed regions" at the surface of serum albumin because the exposed region provide accessibility of the inserted peptide (see middle of page 6) and then lists four specific regions as preferred embodiments. However, listing of the preferred embodiments is not seen as teaching away from residues 360-369 as insertion sites. The '759 publication teaches that "exposed regions" are preferred sites. Residues 360-369 of human serum albumin appear to be exposed regions. The '759 publication relies on the crystal structure of He and Carter (1992) for exposed region determination; He and Carter teach at page 214, the last

sentence of the 1st paragraph under the heading "Discussion" that "a variety of rare, naturally occurring single-site point mutations of HSA identified by anomalous electorphoretic migration are located on the surface of the molecules and exposed to solvent." Instead of listing those exposed sites, He and Carter refer to three earlier published journal articles, one of them i.e. Takahashi et al., (1987, Proc. Natl. Acad. Sci. USA, vol. 84, pages 8001-8005) at Fig. 3 and Table 1 teach a rare, naturally occurring single-site point mutation occurs at residue 365, thus it appears that the art knows residue 365 lies within exposed region as the instant application confirms at pages 35-36. Compare this teaching with the disclosure of the instant application at pages 35-36, where it teaches a heterologous peptide inserted between residues of 364-364 is accessible. Takahashi et al., teach that the point mutation at residue 365 was discovered by Brennan ((Biochim Biophys Acta, vol. 830, pages 320-4, abstract only). In summary, the '759 publication relies on the crystal structure of He and Carter, who teach that amino acid residues 365 is exposed to solvent for exposed regions, therefore it is the Office's position that the claimed residues 360-369 read on "exposed regions at the surface of the molecule" of the '759 publication (see claim 7). The Office maintains that amino acids # 365 of mature human serum albumin had known to be exposed on surface of said serum albumin, thus inserting a heterologous peptide into regions surrounding the exposed sequences either reads on '759 publication or an obvious variation of said publication. Since the entire instant specification is about increasing in vivo stability of a useful therapeutic moiety by inserting the useful therapeutic moiety into a serum albumin and the specification does not teach the unexpected result by

inserting a useful therapeutic moiety into the recited specific region of serum albumin other than being exposed on surface, the specifically recited site is either identical invention as claimed in claim 7 of the '759 publication or an obvious variation of the '759 publication in order to achieve the same effect i.e., "promoting the bioavailability and in vivo stability" of a therapeutic peptide (see the first line of page 6 of the '759 publication).

Applicant further argues that the '759 publication does not show any working example, thus no reasonable expectation of success of being able to insert a biologically active peptide into the recited regions. This argument has also been fully considered but found unpersuasive because the specification at page 9 defines the term "biologically active" refers to something that "may ... provoke an immune response." This definition of biologically active peptide includes everything and no specific biological property is needed to satisfy the instantly claimed invention. Anything inserted in the claimed residues **may** provoke an immune response.

The prosecution history indicates that the Office and applicant both agree that WO 95/30759 teaches an nucleic acid encoding a chimeric polypeptide comprising serum albumin with a useful heterologous peptide inserted in "exposed regions" of serum albumin, wherein the useful heterologous peptide (with various peptide lengths 1-100 amino acids encompassing the size claimed in instant claims 67 for example, see, page 6, line 4 of WO 95/30759) could be derived from various therapeutically useful protein including an angiogenesis-inhibiting proteins (see "tumoral angiogenesis" at page 4 line 9), from a protein or peptide fragments that binds to tyrosine kinase receptor

with various in vivo functional properties (see abstract, page 1-5, last three lines of page 7 to line 7 of page 9, Fig. 1-6, pages 26-30, claims 1-14, 18, 25, and 26). WO 95/30759 also teaches the chimeric polypeptide comprising serum albumin increases in vivo stability and has other desirable pharmacological properties (see page 1). WO 95/30759 teaches various therapeutically useful peptides in claims 3 and 4, at pages 3 and 4, thus covers all of the inserted peptides with either function or name in instant claims 51-57, 59-64. For example, M-CSF (a cytokine, see page 3 line 7 from the bottom of the page of WO 95/30759) binds to a cell surface tyrosine kinase receptor, more specifically bind to an extracellular domain M-CSF-R, thus M-CSF alone teaches limitations of instant claims 53-56, 59. See the abstract of Fixe et al (IDS, AJ, 998, Cytokine vol. 10, 32-7) for description of M-CSF. For example, Zetter (IDS, AK, 1998, Annu Rev Med. Vol. 49, pages 407-24) teaches at abstract that angiostatin and endostatin are well known in the art as angiogenesis-inhibiting proteins useful for fighting cancer, thus angiogenesis-inhibiting proteins useful for fighting cancer described at the top of page 4 of WO 95/30759 anticipates the limitations of claims 51, and 52. "An antibody" at page 3 or "antibodies" in claim 3 of 95/30759 anticipates the limitation "MIRR" in instant claim 57 because MIRR is multi-chain immune recognition receptor according to Castells (1994, Allerg Immunol, vol. 26, pages 127-31). "Antagonist or agonist peptide" at page 4 WO 95/30759 anticipates instant claims 60 and 61. The various functional characteristic in instant claims 62-64 for example is an inherent property of the various heterologous peptides in claims 3 and 4 of WO 95/30759. The in vivo half-life in instant claims 72-74 are inherent characteristic of the

chimeric serum albumin of WO 95/30759. The main reason for inserting heterologous peptides in both WO 95/30759 and instant specification is to increase in vivo half-life. The instant specification is not different from the WO 95/30759 for the in vivo half-life or how the heterologous peptide is inserted in for example, claim 71 of instant claims. See bottom half of page 7 through top of page 8 of WO 95/30759 for comparison of instant claims 70 and 71.

Conclusion

Any rejection set forth in the previous Office action mailed on 7/30/2003 but not repeated in this Office action is either moot or withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne C Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

Misook Yu